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Characterization and validation of a pharmacokinetic model for controlled-release oxycodone

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1 Oxycodone is a strong opioid agonist that is currently available in immediate-release (IR) formulations for the treatment of moderate to severe pain. Recently, controlled-release (CR) oxycodone tablets were developed to provide the benefits of twice-a-day dosing to patients treated with oxycodone. The purpose of this investigation was to develop and validate a pharmacokinetic model for CR oxycodone tablets in comparison with IR oxycodone solution.

2 Twenty-four normal male volunteers were enrolled in a single-dose, randomized, analytically blinded, two-way crossover study designed to compare the pharmacokinetics of two 10 mg CR oxycodone tablets with 20 mg IR oxycodone oral solution. Pharmacokinetic models describing the oxycodone plasma concentration *vs* time profiles of CR tablets and IR solution were derived using NONMEM version IV. The predictive performance of the models was assessed by comparison of predicted oxycodone plasma concentrations with actual oxycodone plasma concentrations observed in a separate group of 21 volunteers who received repeated doses of IR and CR oxycodone for 4 days.

3 The unit impulse disposition function of oxycodone was best described by a one-compartment model. Absorption rate of the IR solution was best described by a mono-exponential model with a lag time, whereas absorption rate of the CR tablet was best described using a bi-exponential model. The absorption profile of the CR tablets was characterized by a rapid absorption component ($t_{1/2}$abs = 37 min) accounting for 38% of the available dose and a slow absorption phase ($t_{1/2}$abs = 6.2 h) accounting for 62% of the available dose. Two 10 mg tablets of oral CR oxycodone hydrochloride were 102.7% bioavailable relative to 20 mg of IR oxycodone hydrochloride oral solution. The population model derived after administration of a single dose accurately predicted both the mean and range of oxycodone concentrations observed during 4 days of repeated dosing. The mean prediction error was 2.7% with a coefficient of variation of 54%.

4 The absorption characteristics of CR oxycodone tablets should allow effective plasma concentrations of oxycodone to be reached quickly and for effective concentrations to be maintained for a longer period after dosing compared with the IR oral solution. The CR dosage form has pharmacokinetic characteristics that permit 12 hourly dosing.

Keywords oxycodone controlled-release

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Introduction

A recent survey of anaesthetists in Finland found parenteral oxycodone to be the most popular opioid for premedication, postoperative pain relief, and sedation in intensive care units [1]. Similar to morphine, oxycodone is a potent opioid agonist with a dose dependent analgesic effect [2], that has proven effective in relieving postsurgical [3] and cancer-related pain [4]. Side effects that have been observed following oxycodone administration are similar to those associated with other strong opioids.

Pharmacokinetic studies have revealed that after oral administration, oxycodone is rapidly absorbed to produce an initial peak plasma oxycodone concentration in about 2 h [5, 6]. Once peak plasma concentrations are reached, oxycodone concentrations rapidly decline, with an apparent terminal half-life ranging from 3.0 to 5.7 h [5, 7]. Because oxycodone is rapidly absorbed and quickly eliminated after oral administration, frequent dosing (every 4–6 h) is required to maintain plasma concentrations within the therapeutic analgesic range.

Recently, controlled-release oxycodone tablets have been developed to extend the duration of action of oral oxycodone and provide the benefits of 12 hourly dosing. In the present study, the pharmacokinetics of oxycodone controlled-release tablets were characterized in comparison with that of an immediate-release oxycodone oral solution. Pharmacokinetic models describing the plasma concentration *vs* time profiles of immediate-release and controlled-release oxycodone after a single dose are presented. The predictive performance of the models was evaluated by comparing the plasma concentrations predicted by the models with actual plasma concentrations measured after 4 days of repeated dosing.

Methods

Study design

Single dose A randomized, single-dose, analytically blinded, two-way crossover design in 24 healthy, fasting, male volunteers was used to compare the pharmacokinetics of two 10 mg controlled-release oxycodone tablets (OxyContin™, The Purdue Frederick Company, Norwalk, CT) with 20 mg of oxycodone administered as an immediate-release oral solution (Roxicodone™, Roxane Laboratories, Columbus, OH). The two treatment phases were separated by a 1 week washout interval. This study was approved by the ethics committee of the contract research organization Hazelton Wisconsin, Inc. All subjects provided written informed consent before participating in the study.

Repeated dosing Twenty-one healthy volunteers received one 10 mg controlled-release oxycodone tablet every 12 h and 5 ml of a 5 mg 5 ml^{-1} immediate-release oxycodone oral solution every 6 h for 4 days in a randomized, analytically blinded, multiple-dose, two-way, crossover study. None of the volunteers who received repeated doses participated in the single-dose study. The methods used in this repeated-dose study have been reported elsewhere [8].

Pharmacokinetic sampling

Single dose During each treatment period, venous blood samples were obtained immediately before study drug was administered (0 h) and at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, 30, and 36 h. Plasma oxycodone concentrations were analysed by GC/MS using naltrexone as the internal standard. The quantification limit of oxycodone in plasma samples was 0.2 ng ml^{-1}, with standard curve linearity between 0.2 ng ml^{-1} and 100 ng ml^{-1}. Inter-day and intra-day precision (expressed as per cent coefficient of variation) ranged from 0.4% to 9.9% for nominal standards ranging from 0.2 ng ml^{-1} to 100 ng ml^{-1}. Oxycodone analysis was performed by The Purdue Frederick Research Center, Yonkers, NY, USA.

Repeated dosing Oxycodone plasma concentrations were determined immediately before the morning dose on days 2–4. In addition, serial blood samples for oxycodone determination were taken for 36 h beginning with the morning dose on day 4. Plasma oxycodone concentrations were analysed as described for the single-dose study.

Pharmacokinetic analysis

The peak plasma concentration (C_{max}) and time to C_{max} (t_{max}) were read directly from individual plasma concentration-time curves. Area under the concentration-time curve from 0 to 36 h (AUC(0, 36 h)) was calculated by the trapezoidal method. The elimination rate constant (λ_z) was calculated by measuring the slope of the linear regression line (log concentration *vs* time) in the terminal elimination phase for each subject. The apparent elimination half-life ($t_{\frac{1}{2},z}$) was calculated from the rate constant. Differences in parameter estimates for the two dosage forms were tested by analysis of variance (ANOVA) appropriate to the crossover design. All analyses were conducted as two-sided tests with alpha equal to 0.05. The SAS® (SAS Institute, Carey, NC) statistical package was used for all ANOVA calculations.

Pharmacokinetic modelling

The plasma concentration-time profiles were characterized with the following general pharmacokinetic model:

$$C_p = f(t) * g(t) \quad (1)$$

where C_p is the plasma concentration at time t, $f(t)$ is the absorption model, $g(t)$ is the unit impulse disposition

function (i.e. the concentration *vs* time profile observed after a unit intravenous dose), and * denotes convolution.

Disposition model The unit impulse disposition function was assumed to be the same for the immediate-release oral solution and the controlled-release tablet and was characterized by a sum of exponentials:

$$g(t) = \sum_{i=1}^{n} A_i \, e^{-\alpha_i t} \quad (2)$$

where A_i and α_i are the coefficients and exponents of the unit impulse disposition function, respectively.

Absorption model The absorption model was assumed to be different for the two preparations. It was assumed that the absorption after administration of the immediate-release oral solution is rapid and could be described by a simple first order absorption process with a lag time:

$$f(t) = k_a \, e^{-k_a(t - t_{lag})} \quad (3)$$

where k_a is the first order absorption rate constant for the immediate-release oral solution and t_{lag} is a lag time. This absorption profile is consistent with previous studies that compared the pharmacokinetics of immediate-release oral solution with intravenous oxycodone [5, 7].

Various absorption models were evaluated for the controlled-release tablet, ranging from multi-exponential absorption models (similar to equation 2) to combinations of multi-exponential and zero-order absorption models. Absorption of oxycodone from the controlled-release tablets was best described by the following bi-exponential absorption model:

$$f(t) = F_{rel}(f_1 k_{c1} \, e^{-k_{c1}(t - t_{lag})} + (1 - f_1) k_{c2} \, e^{-k_{c2}(t - t_{lag})}) \quad (4)$$

where F_{rel} is the relative bioavailability of oxycodone in the controlled-release tablet compared to the immediate-release solution, k_{c1} and k_{c2} are the two first-order apparent absorption rate constants for controlled-release oxycodone, and f_1 denotes the fraction of dose absorbed via the absorption process controlled by the rate constant k_{c1}. The fraction of the dose absorbed via the absorption process controlled by the rate constant k_{c2} is represented by $(1 - f_1)$.

The parametric absorption model for the controlled-release tablet was compared with a nonparametric model derived from deconvolution of the plasma concentrations observed after administration of the controlled-release tablet and the unit impulse disposition function derived from the immediate-release solution. The nonparametric absorption model was represented by a step-wise input model, one step for each interval between the following time points: 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, and 36 h.

Model selection was based on the Log Likelihood criterion ($P < 0.01$) and visual inspection of the fits. The difference in -2 times the Log of the Likelihood (-2LL) between a full and reduced model is asymptotically χ^2 distributed with degrees of freedom equal to the difference in number of parameters between the two models. A decrease of more than 6.6 in -2LL is significant at the $P < 0.01$ level.

Model development

The models were fitted to the data using the nonlinear regression program NONMEM version IV [9, 10]. Data were analysed using population analysis techniques. The population analysis technique recognizes that repeated measures are taken from each individual. The population pharmacokinetic model incorporates subject-specific random effects to characterize the differences in response between individuals and provides estimates of the inter-individual variability in the parameters of the pharmacokinetic model. The population mean pharmacokinetic parameters obtained describe the response in the typical (mean) individual.

Residual variance model The following model was used to characterize the residual error:

$$\log(Y_{ij}) = \log(Cp_{ij}) + \varepsilon_{ij} \quad (5)$$

where Cp_{ij} is the jth plasma concentration of the ith individual predicted by the pharmacokinetic model (equation 1) and Y_{ij} is the measured concentration. The residual departure of $\log(Y_{ij})$ from $\log(Cp_{ij})$ is represented by ε_{ij}. Values of ε_{ij} are assumed to be independently and normally distributed, with mean zero and variance σ^2.

Inter-individual variance model The inter-individual variability in the pharmacokinetic parameters was modelled according to an exponential variance model with the assumption that the pharmacokinetic parameters are log-normally distributed:

$$p_i = \theta \cdot \exp(\eta_i) \quad (6)$$

where p_i is the vector of pharmacokinetic parameters of the *i*th individual, θ is the vector of population mean pharmacokinetic parameters, and $\exp(\eta_i)$ expresses the random difference between θ and p_i. Values of η_i are assumed to be independently multi-variate normally distributed, with mean zero and diagonal variance-covariance matrix Ω with diagonal elements ($\omega_1^2, \ldots, \omega_m^2$). The values of the population parameters θ, σ^2, and Ω were estimated using the so-called first order method in NONMEM.

Model validation To evaluate the predictive performance of the models derived from single-dose administration of immediate-release and controlled-release oxycodone, the plasma concentrations of oxycodone after repeated administration for 4 days were compared with the concentrations predicted by the models. The plasma oxycodone concentrations at 108 h after the start of treatment (last sample) were not included in the analysis because measurable concentrations were only observed in a few individuals. Oxycodone plasma concentrations in the remainder of the subjects were below the quantification limit of the assay, and inclusion

of these samples would have resulted in a biased estimate of the mean prediction error.

The prediction error was calculated to evaluate how well the population pharmacokinetic models predicted the population mean response after 4 days of continuous administration. The log prediction error for a specific measurement was defined as:

$$LPE_{ij} = \log(Y_{ij}) - \log(Cp) \quad (7)$$

where Y_{ij} is the jth measured concentration in the ith individual and Cp is the population mean concentration predicted by the pharmacokinetic model. The population mean response was obtained from a Monte Carlo simulation of 2500 subjects using the parameter estimates (mean and variance) of the population model. Cp for each time point was calculated directly from the simulated data as the logarithmic mean of all simulated concentrations. An estimate of the bias of the model predictions was given by the average LPE. The variance of LPE indicates the variability of the measured concentrations around the population mean prediction. The definition of prediction error according to equation 7 was preferred over the percentage prediction error, $(Y_{ij} - Cp_{ij})100/Cp_{ij}$, because the individual plasma concentration measurements and predictions tend to follow a logarithmic distribution rather than a normal distribution.

The Monte Carlo simulation of 2500 subjects using the parameter estimates (mean and variance) of the population model was also used to evaluate how well the population model predicted the range of observed concentrations after repeated dosing for 4 days.

Results

Subjects

Of the 24 volunteers enrolled in the single-dose study, 23 completed both study phases and were included in the bioavailability analysis. One subject wished to withdraw from the study and was discontinued before the second study phase. The mean age of subjects enrolled in the study was 30 years (range 21–45). Mean height and weight were 179 cm (range 162–191) and 76 kg (range 63–91), respectively.

Pharmacokinetic analysis

Relative to the immediate-release solution, controlled-release oxycodone was 102.7% bioavailable. Based on the 90% confidence interval for the AUC(0, 36 h) ratio's of the controlled-release tablet and immediate release solution (89.5–115.9%), the two formulations were considered equally bioavailable (Table 1). The AUC(0, 36 h) was not significantly different ($P > 0.05$) for the two dosage forms. However, differences in mean C_{max}, t_{max}, and apparent $t_{\frac{1}{2},z}$ were significant ($P = 0.0001$). Figure 1 illustrates the mean oxycodone plasma concentration *vs* time curve for the two dosage forms. As would be expected with a controlled-release formulation, the peak oxycodone plasma concentration was lower after the controlled-release tablet than after the immediate-release solution and plasma levels declined less rapidly after the peak plasma concentration was reached.

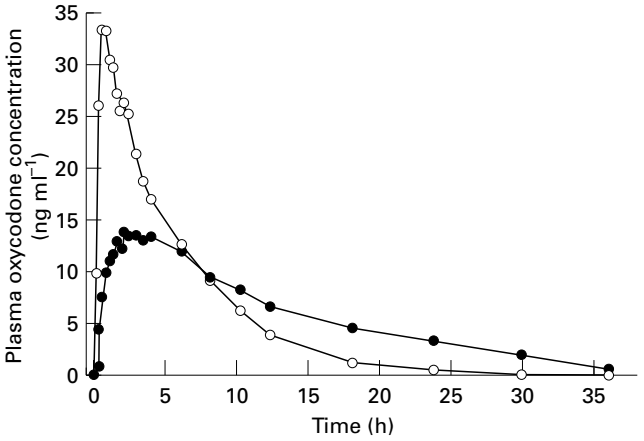

Figure 1 Mean plasma oxycodone concentration *vs* time profiles observed after a single dose of two 10 mg controlled-release oxycodone tablets (●) or 20 mg of immediate-release oxycodone solution (○).

Table 1 Single-dose pharmacokinetics of immediate-release (IR) and controlled-release (CR) oxycodone

	Mean ± s.d.* ($n = 23$)				
Parameter	*20 mg CR oxycodone*	*20 mg IR oxycodone*	*(%) CR/IR*	P†	*90% confidence interval*
AUC (0, 36 h) (ng ml^{-1} h)	199.7 ± 65.3	194.4 ± 23.4	102.7	NS	89.5–115.9
C_{max} (ng ml^{-1})	18.6 ± 6.1	41.6 ± 13.2	44.8	0.0001	32.5–57.0
t_{max} (h)‡	2.62 ± 1.07	1.30 ± 0.63	200.8	0.0001	169.8–232.6
Apparent $t_{\frac{1}{2},z}$ (h)	7.99 ± 2.96	3.21 ± 0.87	249.15	0.0001	216–310.7

*Arithmetic mean. †ANOVA test of significant difference (statistically significant = $P < 0.05$). ‡The range of t_{max} values was 1 to 6 h for CR oxycodone and 0.2 to 2.5 h for IR oxycodone.

Pharmacokinetic model

Immediate-release The combination of a simple, first-order absorption model (equation 3) and a mono-exponential unit impulse disposition function (equation 2) best described the concentrations observed after administration of the immediate-release oral solution. This is consistent with the mean concentration profile observed in Figure 1. For the final analysis, the disposition model was parameterized in CL/F and V_d/F, where CL denotes clearance, V_d is volume of distribution at steady-state, and F is the bioavailability of the oral solution. The actual bioavailability of the immediate-release oral solution was not determined in this study because an intravenous reference dose was not evaluated.

Controlled-release Various absorption models were evaluated for the controlled-release tablet, but only the model that best described the data (as determined by the Log Likelihood criterion and visual inspection) is presented. Absorption of oxycodone from the controlled-release tablets was best described by the bi-exponential absorption model described by equation 4. This model was preferred over a mono-exponential, zero-order drug input, or mono-exponential combined with zero-order drug input. The controlled-release data were best described using the same lag time as for the immediate-release oral solution.

Results of the population analysis are presented in Table 2. The inclusion of separate residual variance terms for the immediate-release solution and controlled-release tablets in the analysis did not significantly improve the fit of the models.

Table 2 Pharmacokinetic parameter estimates for a single 20 mg dose of immediate-release oxycodone oral solution and two 10 mg controlled-release oxycodone tablets

	Population analysis	
*Parameter**	*Mean*	*Variance*
CL/F ($l\,h^{-1}$)	110 (5)	0.045 (0.014)
V_d/F (l)	593 (32)	0.061 (0.017)
k_a (h^{-1})	4.19 (0.58)	1.12 (0.38)
F_{rel}	1.02 (0.09)	0.15 (0.04)
k_{c1} (h^{-1})	1.11 (0.21)	0.25 (0.14)
k_{c2} (h^{-1})	0.110 (0.009)	0.23 (0.09)
f_1	0.38 (0.02)	0.053 (0.043)
t_{lag} (h)	0.206 (0.007)	0.023 (0.012)
σ^2	0.064 (0.005)	

*Based on 912 concentration measurements from 23 individuals. †The square root of the variance is approximately equal to the percentage of inter-individual variability in the pharmacokinetic parameters which is 21% for CL, 25% for V_d, 105% for k_a, 38% for F_{rel}, 50% for k_{c1}, 48% for k_{c2}, 23% for f_1, and 15% for the lag time. ‡σ is approximately equal to the percentage of residual variability which is 25% for the population analysis.

Figures 2 and 3 show oxycodone concentrations predicted by pharmacokinetic models using the typical values of the pharmacokinetic parameters derived from the population analysis as well as the actual concentrations measured after administration of single doses of controlled-release and immediate-release oxycodone. Figure 2 displays the fit for the first 8 h, highlighting the absorption phase. Figure 3 shows the fit over the entire single-dose study period, highlighting the terminal elimination phase.

The cumulative fraction of drug absorbed from the controlled-release tablet following administration of a single dose is shown in Figure 4. The thick solid line represents the median fraction absorbed obtained from a Monte Carlo simulation of 2500 individuals using the population mean pharmacokinetic parameters and their inter-individual variances. The interval in which 80% of the simulated data of the individuals lies (between the 10th and 90th percentiles) is indicated by the thin solid lines.

The bi-exponential absorption pattern of controlled-release oxycodone corresponded closely with the absorp-

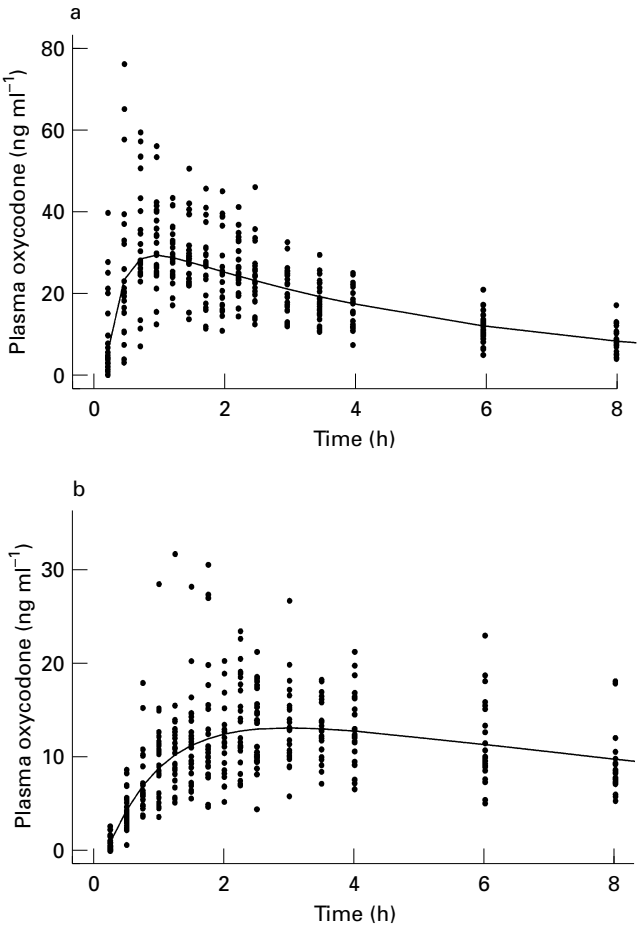

Figure 2 Fit of concentrations predicted by the pharmacokinetic models (solid line) to the actual plasma concentrations (●) during the first 8 h following a single dose: (a) fit of the model linking the mono-exponential absorption function with a one-compartment disposition model following administration of the immediate-release oral solution. (b) fit of the model linking the bi-exponential absorption function with a one-compartment disposition model following administration of the controlled-release tablets.

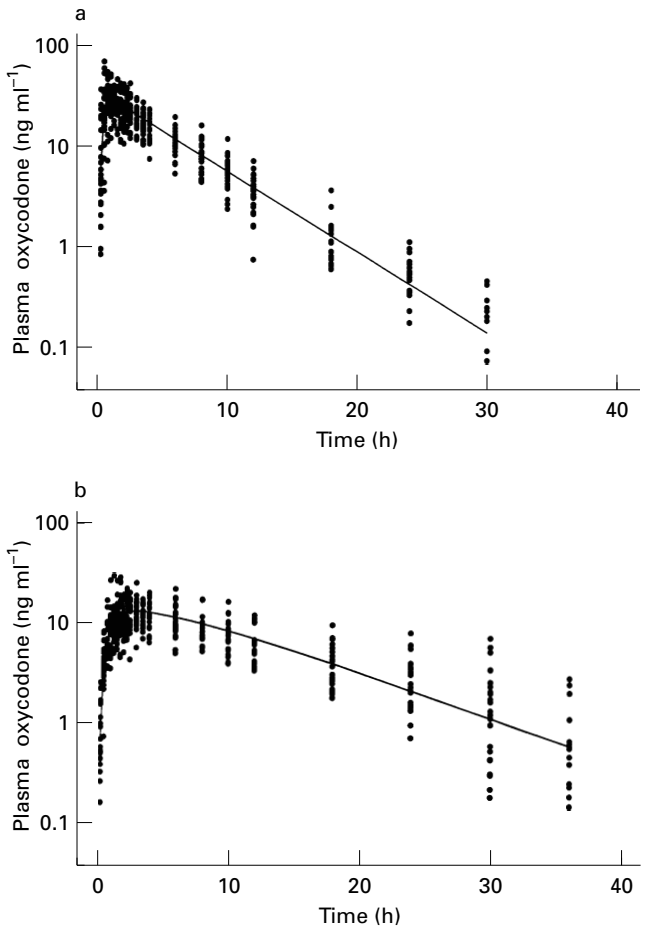

Figure 3 Fit of concentrations predicted by the pharmacokinetic models (solid line) to the actual plasma concentrations (●) during the first 36 h following a single dose: (a) fit of the model linking the mono-exponential absorption function with a one-compartment disposition model following administration of the immediate-release oral solution. (b) fit of the model linking the bi-exponential absorption function with a one-compartment disposition model to the actual concentrations following administration of the controlled-release tablets.

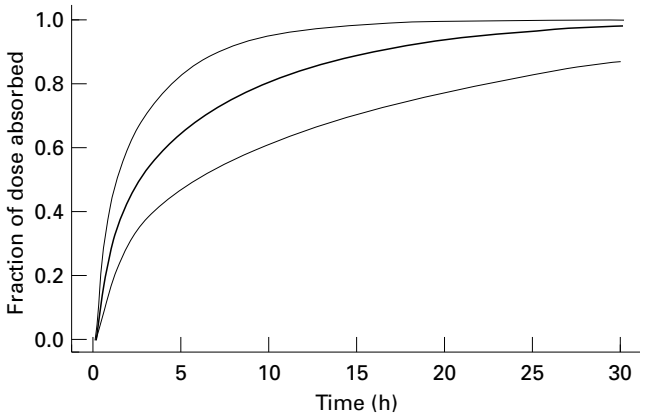

Figure 4 Cumulative amount of drug absorbed from the controlled-release tablet. The solid line in this figure represents the median absorption profile obtained from a simulation of 2500 individuals using the mean pharmacokinetic parameter estimates with associated variances from the population analysis. The thin lines indicate the interval between which 80% of the simulated data lies (between the 10th and 90th percentiles).

tion pattern derived using the non-parametric absorption model (deconvolution data not shown). The nonparametric absorption model, using 11 more parameters, resulted in only a minor improvement of the fit (6.1 points decrease in −2LL), confirming that the derived bi-exponential absorption model is a good description of the absorption profile of the controlled-release tablet.

Predictive performance

The mean and variance of the prediction errors were −0.0061 and 0.291, respectively, for the immediate release solution and 0.0335 and 0.287 for the controlled release tablet. The exponent of the mean *LPE* indicates that compared with the actual mean plasma concentrations, predicted concentrations were on average 0.6% higher for the immediate-release solution and 3.3% lower for the controlled-release tablets.

Figure 5 shows the comparison of the mean oxyco-

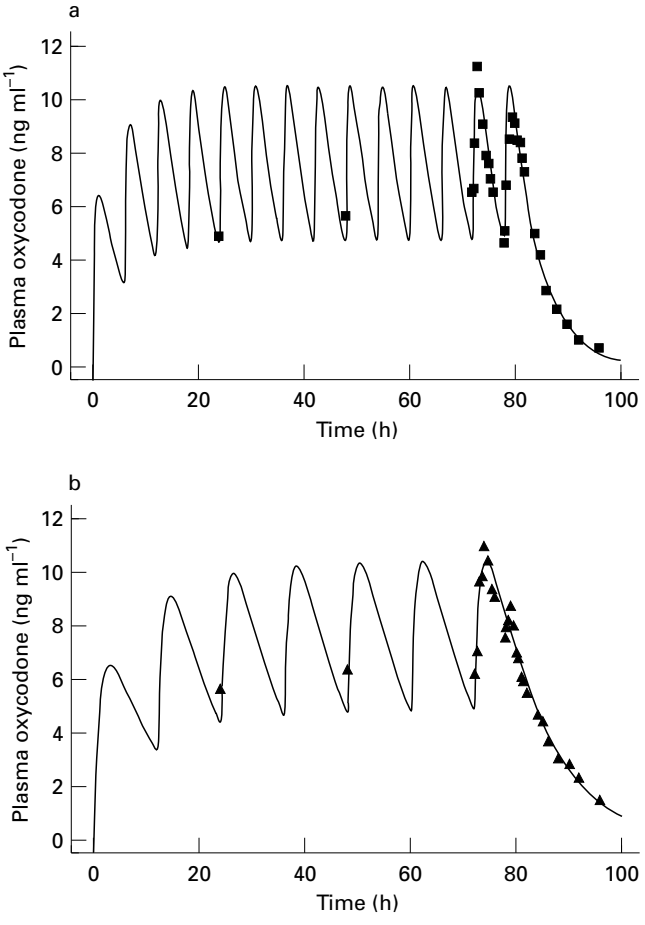

Figure 5 Comparison of the observed population mean oxycodone concentrations (symbols) and the predicted population mean oxycodone concentrations (solid lines) during 4 days of repeated dosing with 5 mg of immediate-release oxycodone solution every 6 h (a) or one 10 mg controlled-release oxycodone tablet every 12 h (b). Model predictions were obtained by a Monte Carlo simulation of 2500 subjects using the parameter estimates from the population analysis following a single dose.

done plasma concentrations observed during the 4 days of repeated dosing and the population mean concentrations predicted by the Monte Carlo simulations using the parameters from the population analysis (all means are logarithmic means). Figure 6 shows the range of concentrations predicted by the Monte Carlo simulations in comparison with the actual observed concentrations. The thin lines cover the region in which 90% of the simulated data lies (5th–95th percentile). The population model predicts the distribution of observed concentrations quite accurately. The simulated 5th percentile actually includes 9.7% of the observed concentrations for the immediate-release oral solution, whereas the simulated 95th percentile includes 93.8% of the observed concentrations (84% of the observed concentrations fall within the two lines). The values for the controlled-release tablets are 6.8% and 98.2%, respectively (92% of the observed concentrations fall within the two lines).

Pharmacokinetic parameter estimates were derived by fitting the pharmacokinetic models to the concentration data observed after repeated administration. Except for the apparent absorption rate constant of the immediate-release solution, all the pharmacokinetic parameters obtained after 4 days of repeated administration were similar to the parameters obtained after single-dose administration. This is consistent with the ability of the pharmacokinetic model derived after a single dose to predict plasma concentrations during 4 days of repeated dosing. The model fitting also revealed that the variability of the observed concentrations around the predicted concentrations was similar after single-dose and repeated-dose administration, 47% and 53%, respectively.

Safety

Seven subjects reported a total of 31 adverse experiences after taking controlled-release oxycodone, and 12 subjects reported a total of 55 adverse experiences after receiving the immediate-release oxycodone solution (Table 3). Most adverse experiences involved the gastrointestinal tract or central nervous system. None of the subjects required medical treatment for an adverse experience. There were no medically significant changes in results of physical examinations or abnormal clinical laboratory findings attributed to study medication. There were no medically significant changes in vital signs observed during the study.

Discussion

We have characterized the pharmacokinetics of oxycodone administered as a controlled-release tablet and compared it with immediate-release oxycodone oral solution. A simple one-compartment model with first-order absorption best described the oxycodone plasma concentration *vs* time profile of the immediate-release oral solution. Absorption of oxycodone from the immediate-release solution was rapid, resulting in a high initial peak concentration. After the peak oxycodone concentration was reached, plasma concentrations declined rapidly. The pharmacokinetic profile of immediate-release oxycodone obtained in this study was consistent with those that have been previously reported [11, 5].

In the present study, oxycodone clearance (CL/*F*) following administration of the immediate-release

Table 3 Adverse experiences following a single dose of controlled-release oxycodone tablets or immediate-release oral solution

Body system *Adverse experience*	*Number of subjects* (number of reports)*	
	Controlled-release	*Immediate-release*
Body		
Headache	4 (9)	3 (12)
Cardiovascular		
Pallor	0	1 (2)
Syncope	1 (1)	1 (1)
Vasodilatation	1 (2)	0 (0)
Digestive		
Nausea	3 (6)	6 (12)
Vomiting	1 (1)	3 (6)
Nervous		
Dizziness	6 (10)	11 (18)
Paresthesia	1 (1)	0
Somnolence	0	1 (1)
Respiratory		
Hiccup	0	1 (1)
Skin		
Sweat	1 (1)	2 (2)
Total	7 (31)	12 (55)

*13 subjects reported one or more adverse experiences. †All adverse events were considered possibly or probably related to study medication.

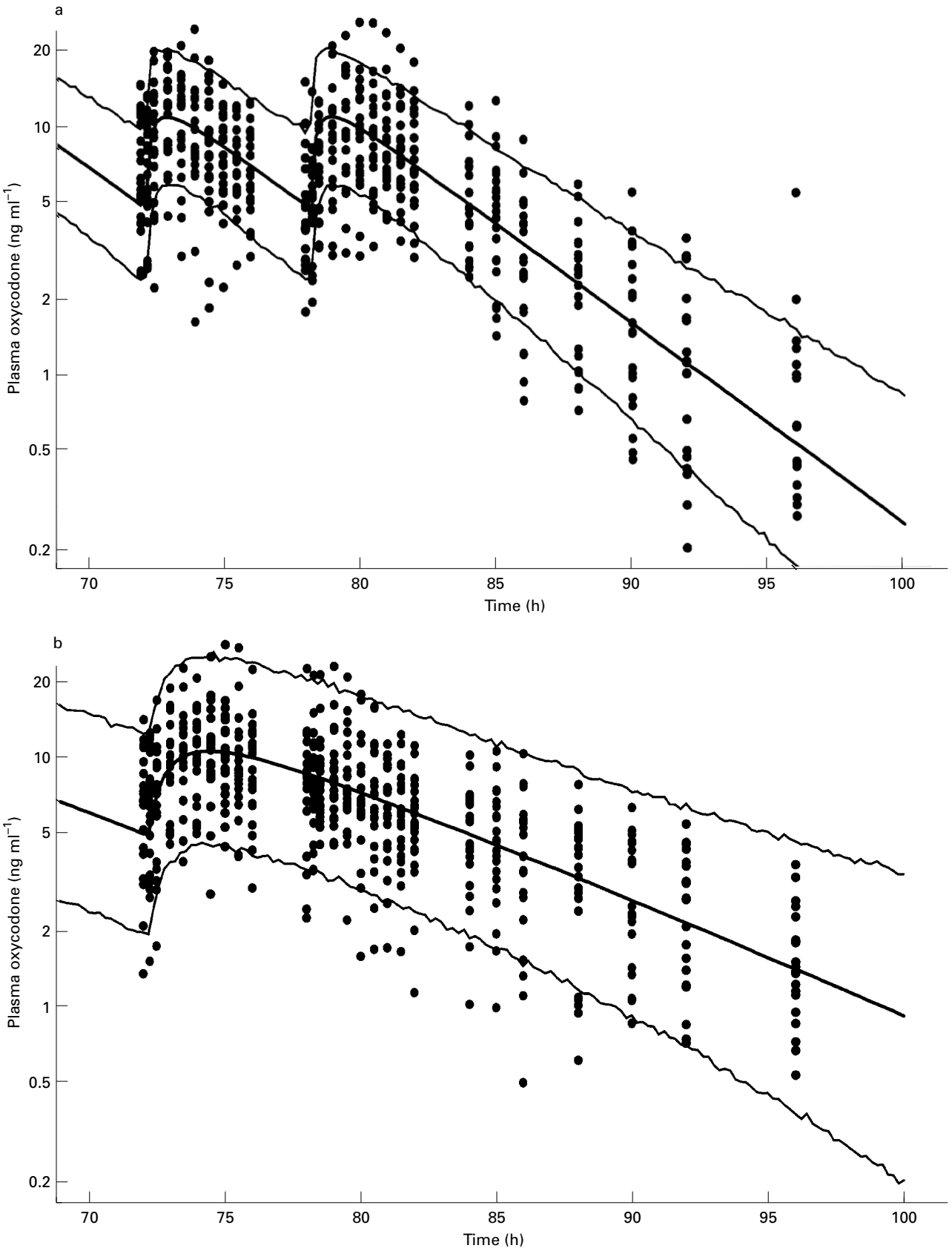

Figure 6 Actual (●) and predicted oxycodone concentrations (solid lines) during the last day of repeated dosing with 5 mg of immediate-release oxycodone solution every 6 h (a) or one 10 mg controlled-release oxycodone tablet every 12 h (b). The thick line is the population mean response obtained from a Monte Carlo simulation of 2500 subjects using parameter estimates from the population analysis following a single dose. The thin lines cover the region in which 90% of the simulated data lies (5th–95th percentile).

solution was slightly higher ($110\,l\,h^{-1}$) than values reported by Pöyhiä *et al.* [11] and Leow *et al.* [5]. However, the differences in oxycodone clearance between this study and previous studies were found to be of no clinical significance when the data were adjusted for body weight ($1.1–1.4\,l\,kg^{-1}\,h^{-1}$).

The bioavailability of oxycodone in the controlled-release tablets was equivalent to that of the immediate-release oral solution. This is supported by the fact that both the nonparametric analysis and the parametric analysis produced similar estimates of bioavailability for controlled-release oxycodone relative to immediate-release oxycodone (Tables 1 and 2).

The absorption profile of the controlled-release tablet was best described using a bi-exponential absorption model, with a rapid initial absorption component ($t_{\frac{1}{2}}abs = 37$ min) accounting for 38% of the available dose followed by a slow absorption phase ($t_{\frac{1}{2}}abs = 6.2$ h) accounting for 62% of the available dose.

The absorption rate constant for the slow absorption phase of controlled-release oxycodone was smaller than the elimination rate constant of oxycodone observed from the immediate-release oral solution data. Consequently, a slower terminal decline in oxycodone plasma concentrations was observed with the controlled-release tablets compared with the immediate-release solution. This should allow for a prolonged duration of analgesic activity. At the same time, the initial rapid absorption phase for controlled-release oxycodone produced a rapid rise in oxycodone plasma concentrations that should ensure a rapid onset of action.

Lower peak oxycodone concentrations after dosing with controlled-release oxycodone were associated with fewer side effects compared with dosing with immediate-release solution at the same total dose. However, these differences were not statistically significant in the data we examined, and whether or not higher peak plasma concentrations observed with immediate-release oxycodone were the cause of the increased number of side effects can not be determined.

The ability of a simple bi-exponential absorption model to characterize the plasma oxycodone profile after administration of the controlled-release tablet is confirmed by the good fit to the data (Figures 2 and 3) and the close agreement between the bi-exponential absorption model and the step-wise input profile determined nonparametrically by deconvolution. The validity of the proposed pharmacokinetic models is also confirmed by the ability of the models to predict the plasma concentrations in a group of different subjects during 4 days of consecutive dosing with the immediate-release oral solution (5 mg every 6 h) and controlled-release tablets (10 mg every 12 h). The population model was able to predict the population mean response in these new individuals accurately. Indeed, considering the inter-individual variability observed after administration of each of the dosage forms, the predictive performance of the proposed models is very good, with a bias of less than 3.5% in predictions of mean oxycodone concentrations based on parameter estimates from the population analysis. Figure 5 shows the close relationship between the observed and predicted mean concentrations for the population model. The population model not only characterizes the population mean response, but also characterizes the variability in plasma drug concentrations between individuals by estimating the inter-individual variability in the pharmacokinetic parameters. The characterization of the distribution of pharmacokinetic parameters in the patient population is crucial for the design of dosage regimens that will ensure that most of the patients receive a safe and efficacious treatment.

The variability in plasma concentrations for both immediate-release and controlled-release oxycodone was within the range expected for oral opioids. The average coefficients of variation of the plasma concentrations around the mean were approximately 47% after administration of a single dose and 53% after 4 days of repeated dosing. There was no difference in the overall variability between the two formulations. Population analysis indicated that about 70% of the variability in plasma oxycodone concentrations could be attributed to inter-individual variability in pharmacokinetic parameters. The greatest variance occurred in those parameters describing the absorption processes. The Monte Carlo simulations showed that the population model derived from the single dose data accurately predicts the distribution of oxycodone plasma concentrations during repeated dosing for four days. The fact that the population model is able to predict both the mean and range of oxycodone plasma concentrations during 4 days of consecutive dosing clearly supports the validity and usefulness of the proposed population model and estimated population parameters.

Comparable plasma concentration profiles were obtained with 10 mg controlled-release tablets every 12 h and 5 mg immediate-release solution every 6 h, suggesting that either formulation could be used for long-term pain management. However, there are fewer peak/trough oscillations and less fluctuation in plasma concentrations during steady-state dosing with the controlled-release tablets. The controlled-release formulation could also offer the convenience of twice-daily administration.

In conclusion, the pharmacokinetics of a newly developed controlled-release oxycodone tablet have been characterized and compared with an immediate-release oral solution. The absorption characteristics of the controlled-release tablet should allow effective plasma concentrations of oxycodone to be reached quickly, and for effective concentrations to be maintained for a longer period after dosing compared with an immediate-release oral formulation, thus allowing dosing every 12 h.

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